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Capecitabine suppresses seizure activity in rats with pentylenetetrazol-induced epilepsy

Effects of Capecitabine on seizures

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Abstract
Aim: Capecitabine was developed as a pro-drug of 5-FU. Epilepsy is a common and often debilitating neurological disease that is characterized by recurrent spontaneous seizures arising from abnormal electrical activity in the brain. The mechanism of the excitatory properties of folates is uncertain, but there is some evidence that they may act by blocking or reversing GABA-mediated inhibition.
Material and Methods: In this study, we investigated the potential anti-folate effects of capecitabine by administering doses of 250 mg/kg IP and 500 mg/kg IP.
Results: We show that capecitabine statistically suppresses seizure activity in EEG telemetry in the brain, prolongs the time to the first myoclonic jolt, and reduces Racine's convulsion score, suppresses folate level and therefore significantly reduces PTZ-induced seizures.
Discussion: It can be assumed that the anti-tumoral mechanism and anti-epileptic mechanism are largely due to the anti-Folate effect in the brain.

Keywords
Capecitabine; Cancer therapy; Epilepsy; Folat level; Brain

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Introduction

Capecitabine is an oral form of 5-FU. For all the side effects of capecitabine, it is similar to 5-FU but has a more appropriate profile [1]. Neurotoxicities seen in 5-FU are rare but serious. Although fluorouracil (FU) is a neoplastic drug, it is an antimetabolite that is frequently used in the treatment of many malignancies such as breast, esophagus, larynx, gastrointestinal and genitourinary system malignancies.

As this drug is cytotoxic, it has systemic side effects such as neutropenia, gastritis and diarrhea. Capecitabine, on the other hand, is a pro-drug of FU, which has been developed in order to have good tolerance through tumor-specific transformation in malignancies and to increase the concentration of intra-tumor drug transit, and is used orally in multiple malignancies [2].

In the study conducted by Zhang et al., it was shown that the CNS penetration of Capecitabine and 5-FU was not sufficient [3]. However, in a study by Michael L. et al., the efficacy of Capecitabin was demonstrated in patients who had previously received systemic therapy (including 5FU) for brain metastasis and developed progression [4] Albeit, it is not known why Capecitabin is more effective in brain metastases than 5-FU.

Epilepsy is a neuronal pathology that results in abnormal episodic increases in electrical activity in certain neurons that can spread throughout the brain. Although our knowledge of epilepsy has expanded significantly over the past 50 years, we are still insufficient to explain its pathophysiology [5].

Antiepileptic drugs are used by 30% of epilepsy patients, but they continue to have seizures and great difficulties in epilepsy treatment. Consequently, it is thought that patients who experience seizures despite antiepileptic use have a refractory or refractory disease [6].

As it is known in the literature, antiepileptic drugs have a narrow therapeutic range, therefore the frequency of side effects is higher. These side effects may occur even in patients whose seizures are prevented by treatment [7].

It was reported that patients using antiepileptic drugs had folate vitamin deficiency and increased epileptic attacks during the administration of folate vitamin therapy to these patients [8]. In experimental studies, it was found that folate is a strong neuro-stimulant and causes more epileptic seizures, especially when applied directly to the nervous system [9].

The mechanism of the neurostimulating properties of folates has not been fully elucidated. However, there is evidence that this occurs as a result of blocking or reversal of GABA-mediated inhibition [10]. The epileptic phenomena caused by folates are similar to those induced by dissulating compounds (Bisuculin, strychnine, penicillin and picrotoxin). However, it differs in many respects from the induction of seizures by neurostimulant drugs (such as Kainic acid, carbachol and neostigmine) [10].

In animal experiments, intravenous (IV) sodium folate administered to animals induces seizure activity only at high doses. However, if the animal is already vulnerable to neurostimulation, or if the blood-brain barrier is damaged due to a local effect (for example, due to heat lesion), the epileptogenic effect of sodium folate administered IV is also reduced. If the blood-brain barrier is bypassed by intraventricular and intra-cortical administration, the convulsive effect is very high in all folate derivatives [9].

Folate-induced epilepsy models can be used to examine the basic mechanisms of epilepsy and the effects and side effects of antiepileptic treatments [9]. However, folic acid increases the kindling pattern of epilepsy and may even be used to directly induce epileptic attacks [10,11].

Low folate levels increase capecitabine-induced toxicity during treatment for colorectal cancer, but the relationship between serum folate level and capecitabine is unknown [12].

Neurotoxicities seen in 5-FU are rare but serious. In this study, we aimed to evaluate capecitabine in terms of folate synthesis and its consequences as an anti-convulsive effects due to folate levels and an anti-tumor mechanism that may be through folate.

Material and Methods

Ethical approval

The experimental methods and analyzes used in this study were approved by the "Experimental Animals and Research Ethics Committee" of the institution where the experiment was conducted. All experiments in our study were carried out in accordance with the ARRIVE experiment guidelines, the Animals Act of 1986, the European Union (EU) Directive 2010/63 / EU for Laboratory Animals and their experiments as per US National Institutes of Health, and the Animal Care and Use Manual.

Experimental animal care

In our study, we used 48 male Sprague-Dawley rats weighing 200-250 g. Forty-eight rats were divided into two groups. The separated 24 rats were randomized to the electroencephalogram (EEG)-based experimental group, and the remaining 24 rats were randomized to the behavior-based experimental group. All rats were placed on a 12-hour light and a 12-hour dark cycle. Light for illumination was provided between 07:00 and 19:00. In quiet rooms, the room temperature was set at 22-24 ° C. The rats were fed standard laboratory food and tap water.

Experimental procedures

In our study, seizures were induced in rats using PTZ, a convulsant chemical. A total of 24 rats were randomized to Group A for the EEG-based experiment and 24 rats to Group B for the behavioral experiment. All EEG recordings and behavioral evaluations were performed according to the previously described protocol [13].

EEG experiment (Group A)

Electrode implantation was performed in rats in Group A to facilitate EEG recording before the experiment. The rats were deeply anesthetized by intraperitoneal administration of 80 mg /kg ketamine and 4 mg /kg xylazine. Then, using precise stereotactic methods, small burr holes were drilled to accommodate the implants in the skull. Polyamide coated stainless steel wires with a diameter of 0.1 mm and a length of 10 mm with an electrical resistance of less than 1Ω were placed as the EEG electrode. The electrodes were placed in the dura on the frontal cortex, 2 mm lateral to the midline and 1.5 mm in front of the bregma. According to previously published protocols, a reference electrode was placed on the cerebellum at a distance of 1.5 mm posterior to the lambda in the middle [14]. Following successful placement, the electrodes were fixed with dental acrylic, a mixture of alloys and hydrocarbons typically used in dental restoration.

After the 12-day recovery period, the rats in Group A were

also randomized equally into 4 groups as follows: Group A1: Control group. No neurostimulant medication was given or intervention was made in this group; Group A2: Placebo group was given intraperitoneal saline; Group A3: Low-gray Capecitabin was given intraperitoneally at a dose of 250 mg/kg; Group A4: Capecitabine was given intraperitoneally at a dose of 500 mg/kg. Pentylenetetrazole (PCT) at a dose of 35 mg /kg (intraperitoneal dose) was administered 30 minutes after Capecitabine or placebo administration to induce seizures in groups A2, A3 and A4. At 35 mg /kg PTZ (intraperitoneal), it results in epileptiform activity on the EEG without observable behavioral changes; EEG changes consistent with the seizure were observed with 70 mg/kg (high dose) PTZ (intraperitoneal). At these doses, EEG signals may be distorted.

The EEG recordings were started 5 minutes after the PCT administration and continued for 60 minutes. The rats were not sedated and were kept awake. EEG recordings were placed in special containers throughout all EEG recordings made with BIOPAC MP150 data collection.

The system is available from Biopac System Incorporated in Santa Barbara, California, USA. We recorded each rat's EEG trace for 60 minutes at a sampling rate of 240 Hz (Hz). The signal was amplified 10,000 times and filtered in the 1-60 Hz range. After recording the EEG, we euthanized the test subject. The presence and severity of seizure activities in our animal model were quantified using the spike-wave percentage method, which is thought to be an ideal way to evaluate epileptiform activity in such studies and has recently been used in experiments. The validity of a sudden increase in the rates of seizures has been investigated and discussed in previous studiesin the literature [15]. EEG interpretation was performed by two blind neurophysiologists to provide quantitative evaluation. To generate a spike-wave percentage score, we split the EEG trace into one-second chunks, and our neurophysiologists evaluated each fragment for the presence of spike waves. The spike wave is defined by the amplitude of the EEG trace at least twice the height of the baseline activity. If there is at least one spike- wave in the next compartment, this segment is considered positive for the presence of spike waves. At intervals of 2 minutes (120 tracks), the number of positive tracks is divided by the total number of pieces (120) to obtain the surge percentage. The overall surge percentage is obtained by averaging the percentages found for every 2 minutes of operation.

Behavioral experiment (Group B)

Twenty-four rats in Group B were evaluated for visually observable seizure activity (Behavioral experiment). Brain electrodes were not placed in this group. As in the EEG experiment, the rats in Group B were randomized into 4 subgroups with 6 rats in each subgroup. Group B1 was an intervention-free control group. Groups B2, B3, and B4 received intraperitoneal PTZ for seizure induction at a dose higher than 70 mg / kg to induce clinically observable seizures.

As in the EEG experiment, 30 minutes after PTZ application, Group B2 was given saline placebo IP, Group B3 received capecitabine at a dose of 250 mg/kg intraperitoneally, and Group B4 received capecitabine at a dose of 500 mg/kg intraperitoneally.

We used two scales to assess the presence and severity of epileptic seizures. The first is Racine's Convulsion Scale (RCS) [15], and the second is the time to first myoclonic contraction (TFMJ). RCS is a simple and reproducible 6-point scoring system for evaluating the epilepsy in rats, as described previously. It is a simple and reproducible 6-point scoring system for eval- uating murine epilepsy. A score of 0 indicates no visible convulsion. A score of 1 indicates twitching of vibrissae and pinnae. A score of 2 indicates motor arrest with more pronounced twitching. A score of 3 indicates motor arrest with generalized myoclonic jerks. In this experiment, the elapsed time (in seconds) upon which a score of at least 3 is obtained represents the rat's TFMJ [13]. A score of 4 indicates tonic-clonic seizure activity while the animal still able to stay on its feet. A score of 5 indicates tonic-clonic seizure with loss of the righting reflex, and finally, a score of 6 indicates a lethal seizure.

The TFMJ is recorded in seconds following the administration of PTZ. In our experiment, almost all animals that demonstrated tonic generalized extension died from seizure activity. The observation period for PTZ- induced seizures were limited to 30 min, similar to previous experiments of this nature in the literature [13]. After this 30- minute evaluation, surviving animals were euthanized.

Results

Results of the EEG experiment

We found that administration of 250 mg/kg Capecitabine significantly decreased seizure activity, as measured via spike-wave percentage compared to a saline placebo (89,8% versus 67,2%, $p < 0.005$). The higher dose of Capecitabine also suppressed seizure activity, with a trend towards greater effectiveness (59,3% versus 89,8%, $p < 0.001$). However, the difference in seizure suppression between the lower and higher dose of LVDP was not statistically significant (Table 1). Representative tracings of the EEG experiment for each subgroup are provided in Figure 1 with higher resolution for better characterization of epileptiform activity.

Behavioral experiment results

The results of our behavioral experiment also suggest that Capecitabine has an antiepileptic effect in our murine model for epilepsy (Table 2). When compared to the placebo-treated group, Capecitabine significantly reduced RCS scores (via the Kruskal-Wallis test) and delayed TFMJ (via one-way ANOVA and post hoc Bonferroni tests). The mean RCS score decreased from 5.1 (which is quite severe, since a score of 6 indicates fatal seizure activity) to 3.8 ($p < 0.05$) with the higher dose of Capecitabine. There was a trend towards lower RCS scores with a higher dose of capecitabine as opposed to a lower dose of LVDP, however, this trend was not statistically significant (Mann-Whitney U test).

Likewise, Capecitabine significantly increased the TFMJ at both lower and higher doses ($p < 0.05$). Compared to the untreated B2 Group with a mean TFMJ of 56.6 s, in the B3 Group with the lower dose of Capecitabine, the TFMJ had increased to a mean of 103.8 s ($p < 0.05$). In group B4 with the higher dose of Capecitabin, the TFMJ had increased to a mean of 168.2 s ($p < 0.01$). The difference in mean TFMJ between lower and higher dose of LVDP was not statistically significant.

Table 1. Results from the EEG experiment

Drugs Group	Spike Percentage
A1 Control	% 0
A2 PTZ (35 mg/kg) and saline	% 89.8 ± 5.9 *
A3 PTZ (35 mg/kg) and 250 mg/kg capecitabine Group	% 67.2 ± 8.01 #
A4 PTZ (35 mg/kg) and 500 mg/kg capecitabine Group	% 59.3 ± 4.06 ##

We randomly allocated 6 rats to each treatment group: A1, A2, A3, and A4. After receiving their respective interventions, the rats in groups A2, A3, and A4 were given pentylenetetrazol (PTZ) at a dose of 35 mg/kg intraperitoneally (IP) to induce status epilepticus. Electroencephalogram (EEG) recording was started 5 min after PTZ administration and continued for 60 min. Surviving animals were euthanized thereafter. The EEG recordings were evaluated by two trained neurophysiologists to look for spike waves in 1-second bins. The spike-wave percentage reflects how many bins contained at least one spike- wave out of the total number of bins available in the EEG records. The higher the spike- wave percentage, the higher the seizure activity. In this experiment, we found that Capecitabine at both 250 and 500 mg/kg IP significantly reduced seizure activity on EEG as measured by spike-wave percentage (# $p<0.05$, ## $p < 0.001$). The further reduction in spike- wave percentage with capecitabine dose escalation from 250 mg/kg to 500 mg/kg was not statistically significant ($p > 0.05$). * $p<0.0001$, A1 compared to A2 and saline group

Table 2. Improvement in RCS and TFMJ with Capecitabine

Drugs Group	Convulsion Stage (Racine)	FMJ onset time (sec)
B1-Control	0	0
B2-PTZ (70 mg/kg) and saline	5.1 ± 0.25*	56.6 ± 3.9 *
B3-PTZ (70 mg/kg) and 250 mg/kg capecitabine	4.5 ± 0.39	103.8 ± 21.05 #
B4-PTZ (70 mg/kg) and 500 mg/kg capecitabine	3.8 ± 0.34 #	168.2 ± 32.4 ##

Similar to the EEG experiment, we randomly allocated 6 rats to each treatment group: B1, B2, B3, and B4. After receiving their respective interventions, the rats in groups A2, A3, and A4 were given pentylenetetrazol (PTZ) at a dose of 70 mg/kg intraperitoneally (IP) to induce behaviorally apparent seizures. In our experiment, Capecitabine at 500 mg/kg IP significantly reduced the Racine's convulsion score (RCS) compared to placebo (# $p<0.05$). In our experiment, Capecitabine at 250 mg/kg and 500 mg/kg IP significantly reduced the time to first myoclonic jerk (TFMJ) compared to placebo (# $p<0.05$, ## $p<0.01$).). * $p<0.0001$, B1 compared B2 and saline group.

Table 3. Improvement in Brain folic acid level with Capecitabine

Drugs Group	Brain folic acid level (nmol/gr)
1-Control	0.69 ± 0.01
2-PTZ (70 mg/kg) and saline	0.78 ± 0.09 *
3-PTZ (70 mg/kg) and 250 mg/kg capecitabine	0.51 ± 0.1 #
4-PTZ (70 mg/kg) and 500 mg/kg capecitabine	0.45 ± 0.06 #

After decapitation, brain folic acid levels were evaluated. Folic acid levels in PTZ (70 mg/kg) and Saline Group were compared PTZ (70 mg/kg) and 250 mg/kg or 500 mg/kg capecitabine Group was significantly decreased (# $p<0.05$)

Discussion

In our study, we planned to investigate the antiepileptic potential of capecitabine, a drug traditionally used in breast cancer, in a rat model. We were motivated to conduct this study as there is new evidence that the pathophysiology of epileptic seizures and cough has overlapping cellular and neurochemical pathways [16,17].

Pre-synaptic and post-synaptic glutamate activity via N-methyl-D-aspartate (NMDA) and other receptors also plays an important role in the pathogenesis of epilepsy [18]. For these reasons, pathways related to GABA and glutamate, the main inhibitory neurotransmitter in the brain, have become common targets of antiepileptics. For example, drugs that increase GABA-mediated inhibition may function as clinically used antiepileptics to treat various syndromes of focal and generalized epilepsy. Glutamate receptor antagonists, both NMDA and non-NMDA, are also potent antiepileptics used in many animal models of epilepsy [19].

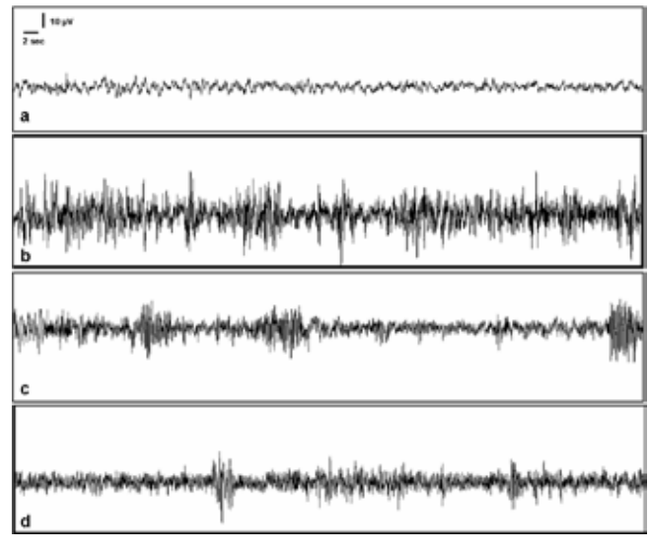

Figure 1. Representative tracings from the EEG experiment. Representative EEG recordings from groups A1 (control), A2 (PTZ and saline), A3 (PTZ and Capecitabine at 250 mg/ kg) and A4 (PTZ and Capecitabine at 500 mg/kg). As expected, there were virtually no spike waves seen in group A1. Dense spike wave activity was seen in group A2 due to the unopposed induction of seizures with 35 mg/kg of IP PTZ, with a mean spike wave percentage score of 89.8 %. There was significant abatement ($p < 0.0001$) of seizure activity—as quantified by spike wave percentages—in groups A3 and A4 with the addition of Capecitabine at 250 mg/kg (A3, 67.2 %) and 40 mg/kg (A4, 59.3%) as compared to A2. However, the marginal improvement seen between groups A3 and A4 were not statistically different from one another.

Some patients using AEDs are at risk for low serum folic acid levels. RBC and serum folate are reduced in 90% of patients taking phenytoin (PHT), carbamazepine (CBZ) or barbiturate. AEDs that do not induce cytochrome P450 enzymes are not associated with low levels of folic acid [20]. Lamotrigine (LTG), an AED with poor folate properties in vitro, has been reported to have no alterations in serum or RBC folate [21]. Serum folate levels in patients using zonisamide (ZNS) were not different from controls [20]. Therefore, low serum and RBC folic acid increase the risk of fetal birth defects in women of childbearing potential. In both men and women, low levels of folic acid are associated with an increased homocysteine and an increased risk of cardiovascular disease. Studies report that routine folic acid supplementation is important for women and men taking AEDs [19,20].

Data on the effects of valproate (VPA) on folic acid are conflicting. Most authors report that valproate does not reduce folate levels, but can interfere with folate metabolism by inhibiting glutamate formyltransferase, an enzyme that mediates folic acid production [22]. Since valproate does not reduce folic acid level, patients using valproate can be included in future studies to see the effects of Capecitabine.

Various AEDs may decrease folate serum levels affecting secondary cerebrovascular events in various epileptic patients [23]. In our study, it was observed that folic acid levels in the brain in the Capecitabine groups decreased significantly

compared to the levels of the PTZ + Saline groups. Normally, folate causes seizures [10], and we think that Capecitabine acts like AEDs by lowering folate levels and possibly halting seizures. According to our data, Capecitabine reduces folic acid in the brain as an AED, and in epilepsy patients taking capecitabine the folate level will likely to decrease significantly for this reason, and patients should probably take folate supplements.

In the EEG data, we observed strong evidence of seizure suppression with aapecitabine. In rats not receiving Capecitabin, fluoride EEG abnormalities were observed, including delta, theta, and spike waves. Treatment with aapecitabine at doses of 250 mg/kg and 500 mg/kg IP resulted in decreased epileptiform activity, and thus we concluded that Capecitabine was effective in alleviating PTZ-induced epilepsy.

Studies conducted with levetiracetam and dextromethorphan showed a decrease in RCS and FMJ and spike percentage in parallel with our study. This suggests the assumption that capecitabine, like these drugs, stops epileptic seizures through GABA inhibition [24].

Folate deficiency in normal tissues is associated with DNA strand breaks, impaired DNA repair, increased mutations, and abnormal DNA methylation, thus making them susceptible to neoplastic transformation. In contrast, if DNA replication and cell division are accelerated, folate deficiency causes ineffective DNA synthesis and ultimately results in inhibition of tumor growth and progression. This mechanism forms the basis of antifolate- based cancer chemotherapy [25].

Notwithstanding that Capecitabine does not penetrate the blood-brain barrier sufficiently, people who develop brain metastases benefit from Capecitabin [4]. Although it is not the primary endpoint of this study, it is also possible that brain low folic acid level due to Capecitabine may be the cause of the antitumor effect Capecitabine on brain metastases.

Conclusion

In conclusion, Capecitabine behaves like an anti-epileptic drug by using its anti-folate effect. Although Capecitabine does not pass the blood-brain barrier well, we think that it is more effective in brain metastases due to its effect on the amount of folate in the brain. Further studies will clarify different effects of Capecitabine.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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